

## REMARKS

The Final Office Action of May 23, 2002 and the Advisory Action of November 26, 2002 have been received and reviewed. Claims 1, 2, 4-14, 16-21, 24-26, 28-32 and 37-58 are pending in the application. All claims stand rejected. Claims 2, 19, 21, 25, 37-40, 42 and 44-58 have been amended and new claims 59-71 have been added as set forth herein. Claims 1, 4-18, 20, 24, 26, 41 and 43 have been cancelled. All amendments and cancellations are made without prejudice or disclaimer. Reconsideration is respectfully requested.

### **I. Double Patenting**

The Final Office Action indicated that if claim 5 were found allowable, claims 6-8 and 41 would have been objected to under 37 C.F.R. § 1.75 as being substantial duplicates thereof. Claims 5, 6-8 and 41 have been cancelled rendering the double patenting objections moot.

### **II. Claim Objections**

Claim 10 was objected to under 37 C.F.R. § 1.75(c) as being of improper dependent format. Claim 10 has been cancelled rendering the objection moot.

### **III. 35 U.S.C. § 112, Second Paragraph**

#### Claims 2, 25, 37-40 and 42

Claims 2, 25, 37-40 and 42 stand rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite for failing to particularly point and distinctly claim the subject matter which applicants regard as the invention. Partially in view of the amendments to claims 2, 38-40 and 42, applicants respectfully traverse the rejections.

Independent claim 2 and claims 37-40 and 42 depending therefrom, as amended, are directed to a recombinant adenovirus with a reduced tissue tropism for liver cells, and independent claim 25 is directed to an adenovirus capsid with a reduced tissue tropism for liver cells. Although applicants do not agree with the statement in the Final Office Action that it is unclear as to what extent the reduced tissue tropism between wild type adenovirus 5 and chimeric

adenovirus for liver cells is “significant,” for the sake of expedited prosecution, applicants have removed the term “significantly” from the claims.

Accordingly, reconsideration and withdrawal of the rejections of claims 2, 25, 37-40 and 42 are requested.

Claim 37

Claim 37 stands rejected under 35 U.S.C. § 112, second paragraph, as assertedly being incomplete for omitting essential steps and resulting in a gap between the steps. Partially in view of the amendment to claim 37, applicants respectfully traverse the rejection.

Claim 37 has been amended to include additional steps in the method. In view of the amendment to claim 37, it should be clear to one of ordinary skill in the art how the method for reducing an adenovirus of a tropism for liver cells is accomplished.

Reconsideration and withdrawal of the rejection of claim 37 is requested.

Claim 10

Claim 10 stands rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Claim 10 has been cancelled rendering the rejection thereof moot.

**IV. 35 U.S.C. § 112, First Paragraph**

Claims 2, 38-40, 44, 45, 51, 52 and 54-57

Claims 2, 38-40, 44, 45, 51, 52 and 54-57 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly containing subject matter which was not described in the specification in such a way to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. Applicants have amended claims 2, 38-40, 44, 45, 51, 52 and 54-57 and in view of the amendments, respectfully traverse the rejections.

Specifically, it was thought that the scope of the claimed invention was very broad and that the few examples provided in the specification were not sufficient to represent the full scope



Serial No. 09/444,284

of the claimed invention. The amendments replace the phrase “gene delivery vehicle” with the phrase “recombinant adenovirus.” Since the specification provides support for the recombinant adenovirus with reduced tissue tropism for liver cells as recited in claims 2 and 38-40 (*See, Specification* as-filed, page 23, lines 25-26 and page 47, Table II, top line) and the recombinant adenovirus with an increased tissue tropism for endothelial cells as recited in claims 44, 45, 51, 52 and 54-57 (*See, Id.* at page 23, lines 19-23 and FIG. 7A), reconsideration and withdrawal of the rejections are requested.

Claims 1, 2, 4-14, 16-21, 24-26, 28-32 and 37-58

Claims 1, 2, 4-14, 16-21, 24-26, 28-32 and 37-58 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification assertedly does not reasonably provide enablement for any gene delivery vehicle comprising at least a tissue tropism for smooth muscle cells, increased tropism for endothelial cells, or with a significantly reduced tissue tropism for liver cells for *in vitro* or *in vivo* gene delivery. Applicants have cancelled claims 1, 4-14, 16-18, 20, 24, 26, 41 and 43 rendering the rejection of these claims moot, amended claims 2, 19, 38-40, 42, and 44-57, and in view of the amendments respectfully traverse the rejections.

As amended, claims 2, 38-40, 42 and 44-57 are directed to recombinant adenoviruses and not to any gene delivery vehicle. Since the application provides support for a cell that produces a recombinant adenovirus having a tropism for smooth muscle cells as recited in claim 19 (*See, Id.*, page 43, lines 22-33), a recombinant adenovirus with an increased tropism for endothelial cells when compared to wild-type virus as recited in claims 44-57 (*See, Id.* at page 39, lines 1-2 and lines 5-8), an adenovirus capsid having an increased tissue tropism for endothelial cells as recited in claim 58 (*See, Id.*), an adenovirus capsid with a reduced tissue tropism for liver cells as recited in claim 25 (*See, Id.* at page 47, Table II), a method of reducing a tissue tropism of an adenovirus capsid for liver cells as recited in claim 37 (*See, Id.*), and a recombinant adenovirus with a reduced tissue tropism for liver cells as recited in claims 2, 38-40 and 42 (*See, Id.*), the claims are enabled.

Accordingly, reconsideration and withdrawal of the rejections of claims 2, 19, 38-40, 42 and 44-57 are requested.

Claim 10

Claim 10 also stands rejected under 35 U.S.C. § 112, first paragraph, as assertedly containing subject matter which was not described in the specification in such a way to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. Claim 10 has been cancelled rendering the rejection thereof moot. ✓

**V. 35 U.S.C. § 102(b)**

Claims 1, 4-8, 11-14, 16, 17, 19, 24 and 41

Claims 1, 4-8, 11-14, 16, 17, 19, 24 and 41 stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by Stevenson et al. Claims 1, 4-8, 11-14, 16, 17, 24 and 41 have been cancelled rendering the rejections of these claims moot. As amended, claim 19 includes the subject matter of claim 20, which was not rejected as being anticipated. Withdrawal of the anticipation rejection of claim 19 is thus requested. ✓

Claims 1, 4-8, 10-14, 16, 17, 19, 24 and 41

Claims 1, 4-8, 10-14, 16, 17, 19, 24 and 41 stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by Wickham et al. Claims 1, 4-8, 10-14, 16, 17, 24 and 41 have been cancelled rendering the rejections of these claims moot. Applicants have amended claim 19 to include the limitations of claim 20, which was deemed not anticipated by Wickham et al. Accordingly, withdrawal of the anticipation rejection of claim 19 is requested. ✓

**VI. 35 U.S.C. § 103(a)**

Claims 1, 4-14, 17-19, 24, 26 and 43

Claims 1, 4-14, 17-19, 24, 26 and 43 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Wickham et al. in view of Stevenson et al. and Woo et al. Claims 1, 4-14, 17, 18, 24, 26 and 43 have been cancelled rendering the rejections of these claims moot. Further, Applicants have amended claim 19 to include the limitations of claim 20, which was not rejected as being obvious. In view of the amendment to claim 19 to include the subject matter of claim 20, withdrawal of the obviousness rejection of claim 19 is requested. ✓

**VII. Lack of Antecedent Basis**

The Advisory Action indicated that claim 21 lacked antecedent basis as depending from canceled claim 1. Claim 21 has been amended to depend from claim 2. In view of the amendment, antecedent basis should be present. ✓

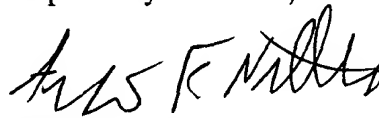
**VIII. Budapest Declaration**

Attached hereto is a Declaration Under 37 C.F.R. §§ 1.801-1.809 signed by Dr. Jaap Goudsmit indicating that the cell line PER.C6 has been deposited under number ECACC 96022940 as well as copies of deposit certificates indicating such deposit. Accordingly, the requirements of 35 U.S.C. § 112 should be satisfied regarding claim 19 which claims the referenced cell line.

**CONCLUSION**

In view of the amendments and remarks presented herein, applicants respectfully submit that the amended claims define patentable subject matter. If questions remain after consideration of the foregoing, the Examiner is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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Date: April 25, 2003  
AFN/afn  
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#25  
PATENT *aa*  
5/6/03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Application of:

Vogels et al.

Serial No.: 09/444,284

Filed: November 19, 1999

For: GENE DELIVERY VECTORS  
PROVIDED WITH A TISSUE TROPISM  
FOR SMOOTH MUSCLE CELLS, AND/OR  
ENDOTHELIAL CELLS

Confirmation No.: 8464

Examiner: S. Chen, Ph.D.

Group Art Unit: 1632

Attorney Docket No.: 2183-4231US

NOTICE OF EXPRESS MAILING

Express Mail Mailing Label Number: \_\_\_\_\_

Date of Deposit with USPS: \_\_\_\_\_

Person making Deposit: \_\_\_\_\_

Declaration Under 37 C.F.R. §§ 1.801-1.809

Commissioner for Patents  
Washington, D.C. 20231

Sir:

I, Dr. Jaap Goudsmit, hereby certify that I am the Chief Scientific Officer of Crucell Holland B.V., successor in interest of INTROGENE B.V. ("Introgene"), and declare that:

1. I am formed and believe that Introgene is the assignee of U.S. Patent Application serial no. 09/444,284.
2. A am informed and believe that on February 29, 1996, Introgene made a deposit of cell line PER.C6 under number ECACC 96022940 under the provisions of the Budapest Treaty with the Centre for Applied Microbiology and Research Authority (European Collection of Animal

Cell Cultures), Porton Down, Salisbury, Wiltshire SP4, OJG, United Kingdom, an International Depository Authority, in accordance with the Budapest Treaty.

3. On behalf of Introgene, I state that all restrictions upon public access to the deposit (except those permitted by 37 C.F.R. § 1.808(b)) will be irrevocably removed upon the grant of a U.S. Patent on this U.S. Patent application, and the deposit will be replaced if viable samples cannot be dispensed by the depository.

4. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the U.S. Code and that such willful false statements may jeopardize the validity of the patent.

Date: 7 Oct 2002

Jaap Goudsmit  
Dr. Jaap Goudsmit

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THE COMPLETE CELL SOLUTION



# **Centre for Applied Microbiology and Research & European Collection of Cell Cultures**

This document certifies that Cell Culture  
(Deposit Ref. 96022940) has been accepted as a patent deposit,  
in accordance with  
The Budapest Treaty of 1977,  
with the European Collection of Cell Cultures on 29<sup>TH</sup> February 1996

*P. J. Packer*

.....  
Dr P J Packer  
Quality Manager, ECACC

BUDAPEST TREATY ON THE INTERNATIONAL  
RECOGNITION OF THE DEPOSIT OF MICROORGANISMS  
FOR THE PURPOSES OF PATENT PROCEDURE

TO

INTERNATIONAL FORM

CRUCELL HOLLAND B.V.  
ARCHIMEDESWEIG 4  
PO BOX 2048  
2301 CA LEIDEN  
THE NETHERLANDS

NAME AND ADDRESS  
OF DEPOSITOR

## I. IDENTIFICATION OF THE MICROORGANISM

Identification reference given by the  
DEPOSITOR:  
PER C6

Accession number given by the  
INTERNATIONAL DEPOSITARY AUTHORITY:  
96022940

## II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION

The microorganism identified under I above was accompanied by:

☒ A scientific description

☐ A proposed taxonomic designation

(Mark with a cross where applicable)

## III. RECEIPT AND ACCEPTANCE

This International Depositary Authority accepts the microorganism identified under I above,  
which was received by it on 29<sup>th</sup> February 1996 (date of the original deposit)<sup>1</sup>

## IV. RECEIPT OF REQUEST FOR CONVERSION

The microorganism identified under I above was received by this International  
Depositary Authority on (date of the original deposit) and  
A request to convert the original deposit to a deposit under the Budapest Treaty  
was received by it on (date of receipt of request for conversion)

## IV. INTERNATIONAL DEPOSITARY AUTHORITY

Name: Dr P J Packer

Signature(s) of person(s) having the power  
to represent the International Depositary  
Authority or of authorized officials(s):

Address: ECACC  
CAMR  
Porton Down  
Salisbury SP4 0JG

Date: 28/2/01

*PJ Packer*

<sup>1</sup> Where Rule 6.4(d) applies, such date is the date on which the status of international depositary authority was acquired

BUDAPEST TREATY ON THE INTERNATIONAL  
RECOGNITION OF THE DEPOSIT OF MICROORGANISMS  
FOR THE PURPOSES OF PATENT PROCEDURE

## INTERNATIONAL FORM

TO

CRUCELL HOLLAND B.V.  
ARCHIMEDESWEIG 4  
PO BOX 2048  
2301 CA LEIDEN  
THE NETHERLANDS

## VIABILITY STATEMENT

Issued pursuant to Rule 10.2 by the  
INTERNATIONAL DEPOSITARY AUTHORITY  
identified on the following page

NAME AND ADDRESS OF THE PARTY  
TO WHOM THE VIABILITY OF STATEMENT  
IS ISSUED

|   |   |
|---|---|
| I. DEPOSITOR  | II. IDENTIFICATION OF THE MICROORGANISM   |
| <p>Name: CRUCELL HOLLAND B.V.</p> <p>Address: ARCHIMEDESWEIG 4<br/>PO BOX 2048<br/>2301 CA LEIDEN<br/>THE NETHERLANDS</p>   | <p>Accession number given by the<br/>INTERNATIONAL DEPOSITARY AUTHORITY:<br/><br/>96022940</p> <p>Date of the deposit or of the transfer:<br/>29<sup>th</sup> February 1996</p> |
| II. VIABILITY STATEMENT   |   |
| <p>The viability of the microorganism identified under II above was tested<br/>on <sup>2</sup>. On that date, the said microorganism was</p> <p><input checked="" type="checkbox"/> <sup>3</sup> viable</p> <p><input type="checkbox"/> <sup>3</sup> no longer viable</p> |   |

- 1 Indicate the date of the original deposit or, where a new deposit or a transfer has been made, the most relevant date (date of the new deposit or date of the transfer).
- 2 In the cases referred to in Rule 10.2 (a) (ii) and (iii), refer to the most recent viability test.
- 3 Mark with a cross the applicable box.

|  |  |
|--|--|
| IV. CONDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED <sup>4</sup>                  |  |
|  |  |
| V. INTERNATIONAL DEPOSITARY AUTHORITY  |  |
| Name: Dr P J Packer<br>ECACC CAMR<br>Address: Porton Down<br>Salisbury<br>Wiltshire<br>SP4 0JG | Signature(s) of person(s) having the power<br>to represent the International Depositary<br>Authority or of authorized official(s):<br><br>Date: 26/2/01 P. Skide |

<sup>4</sup> Fill in if the information has been requested and if the results of the test were negative.